PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
G01N 27/22, 15/05, 22/00
A61B 5/05

A1

(11) International Publication Number: WO 93/18395

(43) International Publication Date: 16 September 1993 (16.09.93)

(21) International Application Number: PCT/GB93/00475

(22) International Filing Date: 8 March 1993 (08.03.93)

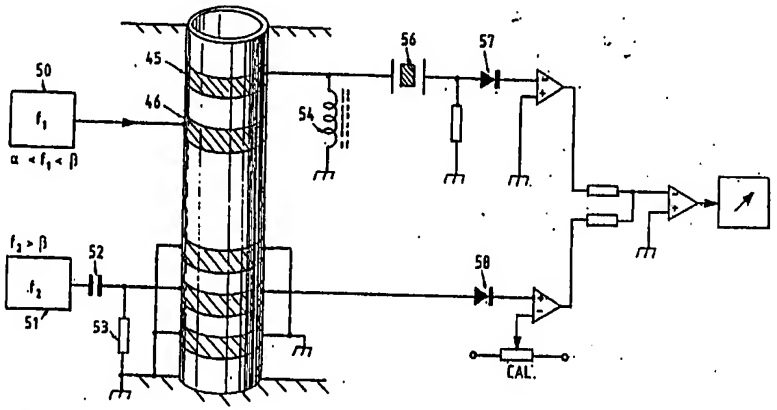
(30) Priority data:
9205175.4 10 March 1992 (10.03.92) GB

(71)(72) Applicant and Inventor: BARNES, Christopher [GB/GB]; "TAN HWFA", Llanllechid, Bangor, Gwynedd LL57 3LA (GB).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.
With amended claims and statement.

(54) Title: APPARATUS FOR DETERMINING THE PHYSICAL AND/OR CHEMICAL PROPERTIES OF A SAMPLE, PARTICULARLY OF BLOOD



(57) Abstract

Apparatus and method for correlating certain physical and chemical properties of blood and other samples by means of remote simultaneous multi-frequency dielectric measurement or when one said frequency is applied and compared with an externally entered parameter proportional to the magnitude of a chosen dielectric parameter at another frequency(ies). Apparatus particularly useful for the near instantaneous assessment of the expected sedimentation condition of red blood cells or other fibrinogen and erythrocyte related parameters.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

APPARATUS FOR DETERMINING THE PHYSICAL AND/OR CHEMICAL PROPERTIES OF A SAMPLE, PARTICULARLY OF BLOOD.

This invention relates to a non-contacting apparatus and method for investigating certain properties of blood such as red cell count, haemoglobin and fibrinogen content ,sedimentation rate and related physical and chemical parameters and for use with similar evaluations in other biological media and for more general use with other samples. In one example the invention is concerned with measurement of fibrinogen to establish instantly the expected sedimentation condition of red cells in blood and certain plasma properties. Throughout this embodiment ,the term " non-contacting" implies a means remote from the sample and the terms "instant" and " instantaneous" imply very near instant with process times only being limited by the speed of electron flow in circuitry, real time electronic calculation and the operation time of electronic display devices.

Protein concentration in biological media is usually assessed by biochemical methods or by methods of physical chemistry such as viscosity measurement and optical rotational dichorism. Also possible are various forms of spectroscopic analysis and chromatography. In one specific situation, that of whole blood, the proteins with the highest concentration are haemoglobin, found in the erythrocyte nuclei and secondly fibrinogen , found dissolved in the plasma. Fibrinogen concentration is medically important, in that in excess it is a non-specific indicator of disease state in a person. Fibrinogen levels manifest their effects in a variety of different ways ; firstly, they effect the

sedimentation rate of the red cells (erythrocytes) giving rise to the so called erythrocyte sedimentation rate or e.s.r. and secondly, they cause effect upon the physical and chemical properties of the plasma.

Manifestations of increased fibrinogen levels have traditionally been monitored in pathology laboratories by two tests, namely; the e.s.r. and the plasma viscosity or p.v. , more recently a third biochemical assay , the so called c-reactive protein or c.r.p. test has also become more popular. E.s.r. tests are however still the most popular with clinicians the World over. The e.s.r. test traditionally uses about 5 milli-litres of venous blood and takes one hour to perform , during which time the red cell fraction (haematocrit) separates from the clearer plamsa fraction and sediments slowly under the control of gravity and internal viscoelastic forces down a capillary tube or a vacutainer containing preservative, this is very time -consuming. P.v. and c.r.p. are also time consuming and because in these latter two tests , the red and white blood fractions have to be physically or chemically separated , there is always the chance , albeit remote, that the operatives might become exposed to viral or bacterial biohazard.

Other blood tests such as cell counting and sizing are also carried out in pathology laboratories using very expensive automated equipment , which needs to sample small quantities of blood in close contact by sucking it through a needle type probe inserted by the equipment into a closed vacutainer. Such cell counters , sometimes referred to as haematological analysers, Coulter or similar, are extremely sophisticated

and operate by application of non-linear electrical field gradients and voltage pulses across individual red or white blood cells which have been located by electric or hydrodynamic focousing in a narrow ,micron sized, orifice or counting/sizing gate. These machines yield a myriad of parameters , upto 23 in some cases, about the state of nearly all the blood components. Nevertheless they are non-portable and extremely expensive and limited by sample throughput and cleansing procedures. Three of the most important parameters outputted by cell counters are perhaps the red cell concentration (r.b.c.) , the mean cell volume (m.c.v.) and the haemoglobin content (Hb). These parameters are considered very useful by many physicians in addition to the e.s.r. value in order to make first diagnoses and general "state of health" assessments. It is considered useful then by the present inventor if such parameters could be provided by a simpler, cheaper, haematology or hamatological analyser technology of greater portability, for use for example in G.P. offices, in the field, or with Third World applications. Of these parameters the problem of haemoglobin has been addressed by previous inventors using optical technology and biochemical lysis of the erythrocytes , however such technology is still quite expensive and because a chemical reaction is involved there is a waiting time before the result is achieved, i:e the output is not instant.

It is thus an object then of one aspect of this invention to provide a means to instantly assess blood fibrinogen levels and their related chemical and physical manifestations remotely and to be be able to monitor , also remotely ,

any or all of the common red cell parameters referred to above, to help preclude biohazard and to provide an analogue or digital readout of all or any of these parameters, in devices that may or may not be configured as a simple form of haematological analyser,and an instant non-optical, non-cell counter means to determine m.c.v., and/or r.b.c and/or Haemoglobin content of blood.

In the case of fibrinogen, it is also an object to provide an output which can be calibrated in units of concentration, or have units which are effectively dimensionless but whose numerical dynamic range scales and correlates according to any or either of the three common methods of fibrinogen assessment referred to above ,or according to a new parameter which the present inventor chooses to refer to as i:s.r. (instant sedimentation rate), but also accounting for and chosen according to the preferance of the physician etc. Automated optical systems have been tried for the assessment of e.s.r. , these are not instant but they do however reduce the time required for a measurement down to circa 20 minutes. Methods where the e.s.r. tube is spinning in order to increase shear forces on the erythrocytes thereby speeding the rate are also possible.

Dielectric methods have also been suggested for the study of time -dependent erythrocyte sedimentation , GB 1574681 (Labora Mannheim). In fact , one purpose of this present embodiment is to provide dielectric systems that advantageously and differently however provide for instant (as opposed to time- dependent) assessment of e.s.r. value as outlined above. Since various dielectric apparatus

has been described in the prior art for making measurements on a variety of samples including even the haematocrit level of blood and in a separate invention,as above, the time dependent sedimentation rate in blood , it is considered very important at this stage in the present embodiment to fully distinguish the prior art from that of this present embodiment. For instance some inventors have described apparatus for making single frequency dielectric and /or conductivity measurements on liquids using two or more electrodes in direct contact with the sample,either tubular. GB 1599241 , where using flowing blood in an insulin/glucose control loop , a 500Hz haematocrit level electrode was formed, or annular and four or six in number disposed in alcoholic liquor ., at d.c. or very low frequency a.c., GB1460892 (Malcolm -Ellis (Liverpool) Ltd;) these were electrically configured like the standard d.c. four point probe conductivity measurement. This has also been used at a.c. by Kell (US 4965206) in a fermenter, where four pointed contacting probes were used. This present invention, quite differently , does not function according to four point probe theory or principles, and re-iterating, a common disadvantage with the above prior art is that the electrodes actually make physical contact with the liquid under investigation. This can give rise to the chance of electrode fouling, electrolytic effects , and the chance of cross-infection and biohazard. Alternatively alternating voltage of contiuously varying (swept) frequency has been applied to a suspension of biological particles, again by means of contacting electrodes, WO85/ 04481 (Public Health Laboratory Service Board). It is possible that swept frequencies could have been utilised for

some of the aims of the present invention however the degree of signal processing which would have been required was considered unacceptably high by the present inventor and the fact that truly "instant" results would not have been available also dismissed this possibility. A further disadvantage of the above invention (WO85/04481) is that it required separate calibration with its cell full of electrolyte in the absence of biological material in some of its aspects. This need for separate calibration is precluded in some aspects of this present invention by the use of differential modes as a specific possibility, which advantageously can offset problems of calibration which may be needed due to environmental and temperature effects. There have also been a few instances in very simple dielectric measurement and control where a single pair of electrodes have been used on the outside of insulating tubes, one such was a "bang /bang" control device for a drip feed machine, EP 0 309 085 A2, (Fischer Scientific Co. , Pittsburg P.A.),where capacitor plates were placed either side of a drip feed tube , if the tube became empty or air-locked, the capacitance fell and finding itself arranged in the feedback loop of a Pierce crystal oscillator (f.e.t. circuit),it caused this crystal oscillator to cease oscillating . This type of prior art is adequate for its purpose, i.e as a warning or on/off control device, but does not have the precision or dynamic range for the applications of this present embodiment. An example of isolated capacitor plates used for actual measurement purposes

with a frequency applied is in the assessment of coal content of fly ash. , GB 2 115 933 A (Kajaani Oy, (Finland)).

Essentially such a system worked by monitoring an a.c. level impeded by the combined capacitive reactance of the plates , the insulating tube and the fly ash.

Similarly, and previously referred to above is the method of Labora Mannheim , where two plate or curved electrodes were attached to a test- tube to monitor time -dependent erythrocyte sedimentation , but in this case their effect was in re-tuning a parallel tuned circuit which effectively formed the input tank to a voltage controlled oscillator. A single inductor wound around the tube could even be substituted for the capacitor plates in that invention , being thence connected in parallel with a separate capacitor and thence to a voltage controlled oscillator. Such oscillators are not considered stable enough for use with this present invention. It was also a pre-requisite of the Labora Mannheim system that there should be a measureable distinction between the dielectric constant of the haematocrit and plasma fractions in all cases. Whilst this may be true in most cases, it is the contention and experience by way of experimental observation of the present inventor that at least in the low megahertz frequency band, this is not always the case for certain pathologies at least. It is unfortunate that Labora Mannheim did not specify the operating range of the v.c.o. employed in their description. The above contention may possibly explain why their invention does not appear to have been widely exploited as an e.s.r. monitor.

Labora Mannheim indicated that a single inductor not in contact with the blood could exploit magnetic as well as dielectric properties , another example of this is EP 0157496A2 (Northern Telecom), which used a coil around a tube connected to a search oscillator (essentially still a v.c.o.), to monitor the flow of magnetic particles in a carrier material.

It is clear then that although the prior art indicates some state of the art techniques, these are niether sensitive enough, stable enough, or fast enough to satisfy the aims of the present invention.

Thus it is a further object of the present invention to provide new and more advanced forms of non-contacting measuring cell ,instant methods and apparatus for remote measurement on blood and other fluids based on dielectric principles where unlike the prior art and advantageously to it, there are provided either preferably two or more single, prefereably non-varying (i:e stable) frequencies are simultaneously applied and employed or where if only one such frequency is applied then an external parameter will be required to be manually or automatically entered into the calculation circuitry to give a satisfactory result hitherto not instantly available by other methods of the prior art . It is a further object to provide new kinds of inductive measurement cell and methods and apparatus for applying the above said frequencies, not hitherto described in the prior art.

Accordingly then the present invention consists of in one aspect , apparatus for determining the physical and/or chemical properties of a sample , blood or other, with

means for retaining the sample, means remote from the sample for applying at least one frequency to the sample , means for measuring the magnitude of the dielectric properties of the sample at each of the said frequencies simultaneously and means for correlating the required physical and/or chemical property of the sample from a simultaneous comparison of the magnitude of a dielectric property of the sample at one of the measuring frequencies with that at the other measuring frequencies or with an alternative parameter proportional thereto. Furthermore accordingly, the said apparatus of this invention consists of non-contacting dielectric measurement cells linked to electronic circuitry through which external parameters can be entered if necessary. Accordingly the method involves inserting and retaining samples, blood or other, in the said apparatus , applying the said frequencies , measuring the said magnitudes and correlating the said required physical and/or chemical parameters , and providing a scaled readable analogue or digital output by means of internal electronic (calculating) circuitry. Often one , two or four frequencies are applied . In the case of two frequencies , one may be between the dielectric alpha and beta dispersions and the other on the high side of the beta dielectric loss maximum, whereas in the case of four all may be on the high side of this beta loss maximum. The method is ideally suited to assessing protein and cellular concentrations in blood and other biofluids but use of other samples is not ruled out. Protein concentration is assessed by its effects on the position and/or magnitude of the high frequency tail of the beta dispersion. Furthermore

as a component of some of the measuring cells available to the said apparatus there are provided circumferential electrode structures spaced lengthwise on a former which is electrically insulating and may double as a tube with one, both or no ends open, into which the separately insulated open or sealed sample tube might be pushed. Furthermore and advantageously, measurement is made either by monitoring the voltage on the transmitting electrode, the receiving electrode or both, whereas previous inventors have only monitored the voltage on a receiving electrode, or used the capacitance of electrodes to resonate in parallel with an inductor, to tune a v.c.o.

In another aspect of the cells and method, structures as those referred to above are employed but assessment is of the number density of red cells by measurement at frequencies in kilohertz regions, and assessment of mean cell volume in blood is also made with frequencies in the low megahertz regions.

In another form the present invention employs structures as above , but a single frequency is used in conjunction with an electronic circuit which uniquely and advantageously allows temperature compensation and entry of an external parameter such as haemoglobin content from another source such as a cell counter or optical haemoglobinometer if the sample is blood, in order to provide a more precise output of fibrinogen content, or fibrinogen related parameter(s). In another form ,the present apparatus and its non -contacting cells are used for assessing changes in the conductivity and /or dielectric constant of a medium

undergoing physical or chemical change e.g.; chemical reaction, bioreaction , biochemical or biotechnological reaction, by following the temporal evolution of the output parameter.

In a further form the present apparatus is used for any of the uses referred to above but the electrode structures are replaced by a single coil or inductor wound around and lying in the plane of the former and where the coil via its effect upon a crystal controls the frequency and amplitude of a variable crystal oscillator (v.x.o.) by series inclusion in the input oscillating tank ,not output load and not feedback, circuit. Advantageously such a method is inherently far more stable than those of other inventors that employed free running types of oscillator and not a v.x.o. Since output frequency of a v.x.o. can be measured by a counter very accurately , down to fractions of a Hertz, there is thus concurrent with the increased stability referred to herein an increased precision and sensitvity over other methods.

In a further aspect of this present invention, a coil structure surounds the apparatus' measuring cell and the coil (inductor) has low impedance tap or link into which power is fed via a coaxial line from an exciter. Any of the assays and samples mentioned herein may be attempted with the invention configured in this way, since the properties of the sample are mathematically or empirically related to the voltage standing wave ratio on the coax line as measured by a reflectometer or v.s.w.r. meter in that line, provided with or without further d.c. amplification.

Yet a further aspect of this present invention is a two frequency measurement cell, method and device, in which a central former is surrounded by four coils or inductors lying coaxially (circumferentially) around it , evenly or not evenly spaced , two of which are non-resonant input (transmit) coils, each sending in a separate single frequency, and two of which receive singly and separately yet simultaneously these original frequencies after passage through the former walls and sample.

In yet a further aspect of this present invention there is operation as per the electrode based two frequency method described earlier but where a signal recovery technique is employed on the low frequency receive electrode which consists of a high Q ferrite cored inductor connected from the electrode to earth which resonates with the electrode self-capacitance, thereby boosting the recovered low frequency signal. This is advantageous because otherwise signals of kilohertz frequencies would suffer very great attenuation after passage through the high impedance of the former and sample holder walls and would thus be virtually undetectable but for this aspect. Those skilled in the art will appreciate that other signal recovery methods such as radio frequency amplifiers and/or phase- locked- loop techniques could also be employed in this context within the scope of the claims of this invention.

It is an observation of the present inventor that the dielectric (capacitive and conductive) facets of a pathological blood sample measured at individual frequencies in the range 10KHz - .1 GHz are related to the general state of health of the individual from which the sample was acquired , thus it is yet one further aspect of this invention to provide means of an electronic general health status indicator based on the observation that there are "norms" of dielectric response at each frequency in the radio frequency continuum and that this can be used with and may contain any of the aforesaid or following aspects of this present embodiment. It is further ascerted by the present inventor that these "norms" arise due to the combined effect of r.b.c., m.c.v., Hb, various other proteins , cell membrane leakiness and plasma electrolyte strength upon the loss peak maxima magnitudes and positions in frequency space of the double or multiple dielectric Beta dispersion of blood , with these dispersive phenomena lying in the approximate frequency range 0.5 - 60 MHz.

In yet a further form the invention in any of its previous embodiments consists of cells, methods , means and devices capable of measuring without contact and without the use of optics some of the physical dimensions and dielectric properties of sample containers , should these vary from container to container if said containers are filled with fluid of constant chemical and physical composition and dielectric property.

In a final aspect of this invention , any of the measuring cells methods, and apparatus referred to herein as belonging to this invention may be operated in a differential mode , i:e using two identical sets of said cells , devices or apparatus with the sample being placed in /measured by one member of said set and a dummy sample, containing for example air, water or electroloyte etc; being placed in /measured by second member of said set. By employing identical components, mechanical and electronic ,in each of the said sets and then connecting them to a differential output stage, this aspect of the present invention allows for the provision of improved results as environmental efects such as temperature will tend to be cancelled by the differential stage.

Although the invention and all its embodiments described herein are primarily illustrated as device(s) for determining protein and cellular concentration in liquids, preferably whole blood without contact , it is not intended to be limited to the precise detail shown , since various modifications could be made therein within the scope of the claims.

The invention and some of the advantages thereof will now be described more fully by way of reference to the accompanying drawings in which;

Figure 1 , illustrates the two frequency measurement cell, with its insulating former and outer annular (circumferential) electrode structure, for use in this invention;

Figure 2 , illustrates the method oi monitoring voltage at the transmit electrode in this invention and shows the stray capacitance path to earth, according to this invention;

Figure 3, is a diagram illustrating the method of signal recovery, for boosting kilohertz signals after passage through the former and sample, according to this invention;

Figure 4 , is a diagram of the alternative measurement cell with an inductor connected to a variable crystal oscillator, for use with this invention;

Figure 5 , is a diagram of the measurement cell , former , tapped coil and device showing manner of connection to voltage standing wavemeter (reflectometer) , according to this invention;

Figure 6, is a diagram of the two frequency four coil measurement cell according to this invention ;

Figure 7, illustrates a block diagram of a two frequency method and device for the measurement of protein , preferably fibrinogen in blood , device can also be used to measure red cell concentration and/or mean cell volume by appropriate adjustment

of frequency pairs according to this invention;

Figure 8 , illustrates a four frequency method and device for the measurement of protein, preferably fibrinogen in blood , according to this invention ;

Figure 9, illustrates the aspect of this invention where a single frequency device is used in conjunction with an external entry parameter to yield a new parameter , where entry parameter is preferably haemoglobin content , to yield fibrinogen content or related parameter, at output if sample is blood, and finally,

Figure 10 , illustrates the differential mode, according to this invention.

Referring to figure 1 , the two frequency measurement cell, 10 and 11 are circumferential transmit electrodes remote from the sample, they are usually, although not exclusively fabricated from thin brass shim. Frequencies f_1 and f_2 are simultaneously passed into 10 and 11 . 12 and 13 are two similar receiving electrodes from which f_1 and f_2 are simultaneously recovered. 14 is a central grounded electrode to minimise stray signal leak along the surface of former/tube 15. 16 and 17 are earthed ground-planes to minimise r.f. radiation from the cell.

Referring to figure 2, the method of measuring voltage at the

transmit electrode ; 18 is a crystal controlled oscillator or similar stable exciter. 19 is a 10 picofarad (or thereabouts) trimmer capacitor , 20 a resistor , usually although not exclusively in the range 5 -25 k ohms , 21 is a signal diode. This method has the advantage that detection is made at a relatively high r.f. voltage. 19 and 20 adjust the effective impedance at the transmit electrode to a value which is easily influenced or changed by introduction of a sample tube containing blood or similar into the orifice 22, this change occurs due to leak of signal to earth and the impedance at the transmit electrode being too high to sustain constant current flow, thus the voltage on this electrode will fall when a sample is introduced. Terminals 23 are thence connected to an electronic voltmeter for interpretation.

Referring next to figure 3, the method of signal recovery for kilohertz frequencies. 24 is a kilohertz frequency generator, presently ,though not exclusively, a 160 kHz sine -wave and 25 is the receiving electrode whose self-capacitance 26 brings about high Q resonance with ferrite cored inductor 27 in order to boost the recovered signal appearing for detection at 28.

Reference to figure 4 shows the alternative measurement cell and single frequency v.x.o. method used with this present invention. Coil 30 is wound around former 29 and is connected in series with crystal 31 to form the input tank circuit of v.x.o.(variable crystal oscillator) 32. The output frequency and amplitude of 32 will differ

when 29 is empty and when 29 contains a sample in its own tube. They will also differ from sample to sample and will drift if any of the sample properties is temporally unstable. Thus physical and chemical properties of sample may be related to amplitude and frequency of 32 . Method is superior to those inventions which have used a v.c.o. due to inherently higher stability of a v.x.o., and is superior to those which have used coil in feedback circuit of crystal oscillators for simple on/ off bang/bang control.

Reference to figure 5, shows continuous wave v.s.w.r. method where 33 is an inductor but where an essential feature of which is a low impedance tap point or a link. 33 resonates with a capacitor , either self capacitance of inductor and former or external additional parallel capacitance . Power is fed into 33 from exciter 35 via reflectometer or voltage standing wave meter 34. 34 may or may not require d.c. amplification. When sample tube is pushed into orifice of former, resonant frequency of system alters slightly , causing an alteration in the amount of power absorbed by 33 and reflected back towards 35 , the change in this reflection or v.s.w.r. is sensed and measured by 34, thus the reading of 34 relates to physical and chemical properties of the sample, within this definition is covered temporal instability of a sample.

Reference to figure 6 , shows the inductive variant of figure 1 , a two frequency four coil measurement cell used in this invention. Power is passed in at two frequencies f_1 and f_2 simultaneously by non-resonant link inductors 37 and 38 respectively. Said frequencies are recovered after passage through the former ,sample tube and sample by resonant recovery at parallel tuned circuits 39/41 and 40/42. Any chosen degree of mathematical comparison , calculation or processing then follows on the voltages v_1 and v_2 depending on the precise application and sample type.

Reference to figure 7 shows a specific use of the invention as a device, in block diagram form, preferably for the measurement of fibrinogen in blood . Frequency f is on the high frequency tail of the dielectric beta dispersion (usually although not exclusively around 50 MHz). 48 and 49 , 51 and 52 , 47/49 and 58 operate exactly as in accordance with the equivalent parts in the voltage monitoring system described in figure 2.

In the case of blood , the detected voltage is related to the total protein content being mainly haemoglobin and fibrinogen. Frequency f lies between the alpha and beta dispersions and 45, 46 , 50 and 54 operate exactly as in accord with their equivalent counterparts in the kilohertz frequency recovery method described by reference to figure 3. However , 56 is an extra component which takes the form of a series quartz crystal or similar filter to remove any traces of high frequency signal which may have strayed into this part of the circuit where it is unwanted. The voltage at the detector

57 is related to the number density of erythrocytes, if sample is blood, and this number density in turn correlates to a large extent with sample haemoglobin content, for the vast majority of pathological samples (private study of the present inventor). Said voltage at 57 is also weakly dependent on haemoglobin concentration direct and also on mean cell volmue according to a complex mathematical function involving both. Thus appropriate mathematical manipulation of the signals from detectors 57 and 58 in circuit 59 (at its simplest comprising two operational amplifiers) can remove an approximate contribution due to haemoglobin from the total protein function, to leave remaining a signal contribution which depends mainly on fibrinogen levels. The output scale factor may be arranged to yield an output parameter which the present inventor chooses to refer to as the i.s.r.(instant sedimentation rate),if the sample is blood, this parameter may be scaled in magnitude and dynamic range of the more traditional e.s.r., a parameter which physicians are more used to interpreting. Those skilled in the art however will appreciate that there is no reason why the output should not be scaled in order to give an "instant " p.v. reading or an "instant" c.r.p. reading covering the equivalent dynamic ranges of these two parameters and indeed this is within the scope of the present claims herein.

Referring next to figure 8 , this illustrates a block diagram of the four frequency cell, measurement method and device for use

with this present invention. Because different parts (in frequency space) of the high frequency tail of the dielectric beta dispersion are influenced in different ways by different proteins, e.g. haemoglobin and fibrinogen, if the sample is blood, it is possible to obtain an estimate of fibrinogen levels by simultaneous four frequency dielectric measurement in the frequency range 15 -60 MHz (usual but not exclusive range within scope of this present invention). Usually frequency f_1 is of the order of 17 MHz, f_2 is of the order of 20 MHz , f_3 is of the order of 30 MHz , and, f_4 is of the order of 50 MHz. Frequencies f_1 - f_4 are passed in through electrodes 60-63 and out through 65-68 inclusive. 69-72 are narrow band-pass filters centered on f_1 - f_4 respectively to assist with signal recovery. 73 is an analogue divider which divides the detected voltage from the 17 MHz filter and detector by that derived for the 20 MHz signal . Likewise , 74 performs a similar operation for f_3/f_4. For blood as a sample, output functions of 73 and 74 have similar components in repect of Heamoglobin but somewhat different for fibrinogen, then wieghted subtraction in 75 tends to enhance the effect of fibrinogen and suppress the effect of haemoglobin. At this point in the circuit the fibrinogen function is almost linear but is superimposed on a d.c. level , thus an appropriate offset is provided by 76 so that the output parameter may be displayed at 77. Those skilled in the art will appreciate that the technique is not limited within the scope of the claims to only blood as a sample and indeed any system containing cellular biomass and protein together or even mixtures of proteins will be amenable to this kind of treatment. When the sample is

blood , this aspect of the invention is a most accurate way of determining fibrinogen but because four frequencies are employed , very careful adjusment and initial calibration initially with pathological samples and latterly with electrolyte solutions is necessary and temperature compensation of 73-76 is also desirable. Thus this aspect of the invention is technologically challenging.

Referring next to figure 9 , the block diagram of the aspect of the invention concerned with fibrinogen or protein assessment when a numeric entry parameter (e:g haemoglobin) is available or known. If Haemoglobin content of blood is known or available from another source such as Coulter or similar cell counter or biochemical optical haemoglobinometer, and is used as the said external entry parameter then the invention configured according to this aspect can be used to provide a simpler and more accurate assessment of fibrinogen level. Referring then to the drawing , the main component parts of the system 78-81 operate in exactly the same accord as their equivalent parts indicated in figure 2. The digital voltmeter 84 is used with a differential input and temperature is compensated for using potentiometer 82. Those skilled in the art will appreciate automatic compensation also to be possible within the scope of the present claims. 83 ,the Haemoglobin entry circuit is also shown for simplicity as a potentiometer, but in reality in the working demonstrator instrument it comprises of a set of rocker or thumbwheel type

switches and it is usually adequate to enter the Haemoglobin value to the nearest whole unit. Those skilled in the art will appreciate that there are several other means of haemoglobin entry, both analogue and digital within the scope of the claims of this present invention, including for example; acquistion of the haemoglobin level by direct connection to the electronic circuitry of a cell counter or haemoglobinometer. The action of the system is achieved because the voltage at 81 is an inverse function of the total protein content and the differential action of 84 removes from this the haemoglobin contribution and simultaneously allows addition of the temperature compensation voltage. Those skilled in the art will appreciate that the invention configured according to this aspect could be used with multicomponent fluid systems other than blood within the scope of the claims of this invention, and that if manually acquired e.s.r. value were available instead of haemoglobin that the system could be configured "in reverse" to yield a heamoglobin value at its output , within the scope of these present claims. Those skilled in the art will appreciate that simultaneous frequencies may be applied through just one electrode or inductor , within the scope of the claims of this present invention by using power combiners and/or directional coupling techniques.

Another feature which should not be overlooked when employing any of the said cells ,means, methods and devices referred to in this present embodiment and by way of reference to the drawings is that when the sample is contained in its own container , said container being a tube, vacutainer , capillary etc, with open or sealed end(s) , aforesaid container

should be a snug push fit into former /tube of said cell etc; figures 1-9, and there should not be excessive slack or excess air gap (although not all the air is displaced) between this container and the former inner walls. If the container dimensions vary (from container to container) , particularly the internal and external diameters, then errors in the measurement produced by methods and devices herein may arise. Such errors arise from variations in the air gap capacitance where the air gap is that between the said container and former. It will however be appreciated by those skilled in the art that such errors can be reduced/corrected for manually or automatically by tube size correction techniques. Furthermore they will appreciate that this problem may be turned on its head to yield yet a futher aspect of the invention referred to above and in the claims herein , namely that if samples of fixed chemical and dielectric property are employed in sample containers of nominally the same size but with slight variations in size or dielectric property, then said cells , methods , means and devices may be used to measure a physical dimension of sample container without the use of a rule, calipers , micrometer other gauges or optics.

Referring finally to figure 10, 85 is the sample tube and 87 is the dummy or control sample tube. 86 & 88 are identical formers as illustrated in any of the prior drawings in this present embodiment. 89 & 90 are identical electronic circuits associated with any of means ,methods and devices

in this invention. 91 is a difference amplifier and 92 an appropriately scaled output device/ display. Effects of temperature and other environmental factors tend to be cancelled by this arrangemnet , thus making the invention according to this aspect more stable and accurate than those previous disclosures which do not employ a differential mode.

Throughout this embodiment, the sample by way of example has been considered to be on the whole stationary in a closed or open ended sample tube. Nothing in this embodiment prevents the sample from being a flowing or moving sample, in which case the formers referred to in every aspect herein would then be of the variety with both ends open. Furthermore, it will be appreciated by those skilled in the art, that the aforesaid formers could be fabricated in a "turned inside out" manner i:e with their electrodes or inductors disposed of on the inside and with their ends closed to prevent fluid entry or contact with said electrodes or inductors, thus forming probes which could then be dipped into samples otherwise retained, but yet with operation in accordance with the claims of this present invention. Furthermore , throughout this present embodiment, reference has been made so far exclusively to non-contacting systems mainly to emphasise their obvious advantages , however those skilled in the art will appreciate that it is hereby also disclosed that the new methods means devices etc. herein can also be made to work when there is contact with the sample material by minimal modification." Furthermore, those skilled in the art will appreciate that all

the said cells ,methods ,means and devices referred to herein may be provided with manual or automatic means of sample mixing handling, labelling etc; and results, analogue or digital, could also be computer stored or on a print-out, and samples may or may not be aspirated from their original containers into second or subsequent containers.

Furthermore, nothing in this present invention prevents the sample from being biomaterial in vivo, small e.g. cells or large e.g. human body digits, limbs etc.

Furthermore those skilled in the art will appreciate that there is scope for modification in the aspects of the embodiment that refer to simultaneous multi-frequency excitation and reception since digital as well as analogue methods can be used here and pseudo instantaneous output may be obtained by using fast frequency steps or sweeps of frequencies applied to transmit electrodes. Furthermore in all aspects where diode detection is employed within this present embodiment, see particularly figures 2 and 3 and figures 6-9, this can be replaced by phase sensitive detection as a viable alternative with the dual consequence of added sensitivity and two component information from the real and imaginary part analysis, advantageous since in reality samples exhibit complex dielectric behaviour and dielectric constant , sometimes referred to as permitivity has such real and imaginary parts . For a said sample dielectric property the present inventor states the real part of permitivity is a measure of the sample a.c . capacitance and with the present invention the apparatus using circumferential electrodes will respond mainly to this capacitive facet, whereas that using coils will respond more strongly to the imaginary part of the permitivity (loss) or conductive facet.

CLAIMS

1. Apparatus for determining the physical and/ or chemical properties of a sample , comprising means for retaining the sample , means remote from the sample for applying at least one frequency to the sample , means for measuring magnitude of dielectric properties of the sample at each of said frequencies simultaneously , and means for correlating required physical and /or chemical property of the sample from a simultaneous comparison of the magnitude of said dielectric property at one of the measured frequencies with that at the other measured frequencies or with an alternative parameter proportional thereto.

2. Apparatus according to claim 1, where said frequencies are stable and non-varying.

3. Apparatus according to claim 1, where said frequencies are applied through circumferential electrodes spaced in line.

4. Apparatus according to claim 1, where said frequencies are received after passage through sample by circumferential electrodes.

5. Apparatus according to claim 1, where said frequencies are applied through inductors.

6. Apparatus according to claim 1, where said frequencies are applied by link coupled inductor(s) connected to an exciter via a voltage standing wave meter (reflectometer).

7. Apparatus according to claim 1, where said frequencies are applied through tapped inductors.

8. Apparatus according to claim 1, where said frequencies are applied by a variable crystal oscillator (v.x.o.).

9. Apparatus according to claim 1, where said frequencies are received at parallel resonance .

10. Apparatus according to claim 1, where said frequencies are received as reflected power in a low impedance line, after reflection from link coupled inductor.

11. Apparatus according to claim 1, where said frequencies are received as reflected power in a low impedance line, after reflection from a tap coupled inductor.

12 . Apparatus according to claim 1, where means for measuring magnitude of dielectric properties involves r.f voltage measurement and/or d.c voltage measurement after detection, said voltage arising from receive electrodes and /or inductors.

13. Apparatus according to claim 1, where means for measuring magnitude of dielectric properties involves measurement of voltage levels at transmit electrodes.

14. Apparatus according to claim 1 and 8, where means for measuring magnitude of dielectric properties involves monitoring output frequency of said v.x.o.

15. Apparatus according to claim 1 and 8, where means for measuring magnitude of dielectric properties involves monitoring amplitude output of said v.x.o.

16. Apparatus according to claims 1, 6 and 10, where means for monitoring magnitude of dielectric properties involves measuring voltage standing wave ratio in feed line to link.

17. Apparatus according to claims 1, 7 and 11, where means for monitoring magnitude of dielectric properties involves measuring voltage standing wave ratio in feed line to tap.

18. Apparatus according to claim 1, where said magnitude is mainly that of capacitive facet of dielectric property at each simultaneous measurement frequency.

19. Apparatus according to claim 1, where said magnitude is mainly of conductive facet of dielectric property at each simultaneous measurement frequency.

20. Apparatus according to claim 1, where said magnitude of dielectric properties is dependent on both capacitive and conductive facets of sample.

21. Apparatus according to claim 1, wherein said means for correlating physical and/or chemical properties of sample from simultaneous magnitude of comparison of dielectric property at one measured frequency with that at other(s) is achieved by internal electronic circuit.

22. Apparatus according to claim 1, where correlation of said properties from said simultaneous comparison of magnitude of dielectric property at one measured frequency with alternative parameter proportional to said magnitude at other frequencies employs an electronic cicuit for manual entry of said alternative parameter.

23. Apparatus according to claim 1 and claim 22, as per claim 22 ,except where said electronic circuit permits the automatic entry of said alternative parameter from an external source e.g. cell counter and/or haemoglobinometer.

24. Appparatus as in claim 1, operated in a differential mode.

25. Method for determining the physical and /or chemical properties of a sample employing apparatus as in claim 1 , comprising the steps of; inserting /retaining the sample, applying at least one frequency, correlating chosen physical and/or chemical property of sample from simultaneous comparison of magnitude of desired dielectric property as at one of applied frequencies with that at other (simultaneous) measurement frequencies or with alternative parameter proportional thereto, then scaling and reading instantaneous output parameter which is correlate of required physical or chemical property.

26. Method according to claim 25 above, wherein the sample is blood.

27. Method according to claim 25, wherein the sample is any blood fraction and /or component.

28. Method according to claims 25 and 26, wherein the correlate parameter is any or all of the following: red cell count (r.b.c.); mean cell volume (m.c.v.); haemoglobin contnet (Hb) ; fibrinogen content or any or all of fibrinogen related parameters namely; e.s.r., p.v. , c-reactive protein and i.s.r.

29. Method according to claim 25, where the sample is biofluid other than blood.

30 . Method according to claim 25, where the sample is a liquid other than biofluid.

31. Method according to claim 25 and 26 but where the output is scaled in arbitary units of "general health status indication".

31. Method according to claim 25 where the sample is a composite comprising a liquid of constant physical chemical and dielectric property and an insulating tube /holder where thus said required correlate becomes a physical dimnsion of tube/holder.

32. Method according to claim 25 where the sample is a digit of the human body.

33. Method according to claim 25 where the sample is a limb of the human body.

AMENDED CLAIMS

[received by the International Bureau on 23 July 1993 (23.07.93); original claim 1 amended; claims 25-34 replaced by amended claims 29-38 new claims 2-5, and 39-45 added; claims 2-24 renumbered as claims 6-28 wherein claims 9,13,16,18,19 and 22-26 are amended (7 pages)]

1. Apparatus for determination of the physical and/ or chemical properties of a sample , comprising means for retaining the sample , and comprising a chosen measuring cell and comprising means of correlating said physical and/or chemical properties of sample from two or more parameters , where said two or more parameters comprise of magnitudes of dielectric properties of sample arising from simultaneous measurement at various measurement frequencies and /or an externally entered parameter whose magnitude is proportional to the sample dielectric property(ies) at alternative measurement frequency (ies).

2. Apparatus as in claim 1 wherein the said determination is instant.

3. Apparatus as in claim 1 wherein the said determination is contactless, i:e without direct electrical contact to the sample.

4. Apparatus as in claim 1 ,where the said various frequencies are in the range above 10 KHz and below 1000 MHz.

5. Apparatus as in claim 1 where the said correlation occurs simultaneously with frequency application and dielectric property measurement.

6. Apparatus according to claim 1, where said frequencies are stable and non-varying.

7. Apparatus according to claim 1, where said frequencies are applied through circumferential electrodes spaced in line.

8. Apparatus according to claim 1, where said simultaneous frequencies are received after passage through sample by circumferential electrodes.

9. Apparatus according to claim 1, where said simultaneous frequencies are applied through multiple inductors.

10. Apparatus according to claim 1, where said frequencies are applied by link coupled inductor(s) connected to an exciter via a voltage standing wave meter (reflectometer).

11. Apparatus according to claim 1, where said frequencies are applied through tapped inductors.

12. Apparatus according to claim 1, where said frequencies are applied by variable crystal oscillator (v.x.o.).

13. Apparatus according to claim 1, where said frequencies are received at parallel resonance .

14. Apparatus according to claim 1, where said frequencies are received as reflected power in a low impedance line, after reflection from link coupled inductor.

15. Apparatus according to claim 1, where said frequencies are received as reflected power in a low impedance line, after reflection from a tap coupled inductor.

16. Apparatus according to claim 1, where means for measuring magnitude of dielectric properties at each simultaneous frequency involves simultaneous r.f. voltage measurement and/or d.c voltage measurement after detection, said voltage arising from receive electrodes and /or inductors, after frequency selective (filtered) recovery.

17. Apparatus according to claim 1, where means for measuring magnitude of dielectric properties involves measurement of voltage levels at transmit electrodes.

18. Apparatus according to claim 1, where means for measuring magnitude of dielectric properties involves monitoring output frequency of said v.x.o.

19. Apparatus according to claim 1, where means for measuring magnitude of dielectric properties involves monitoring amplitude output of said v.x.o.

20. Apparatus according to claims 1, 10 and 14, where means for monitoring magnitude of dielectric properties involves measuring voltage standing wave ratio in feed line to link.

21. Apparatus according to claims 1, 11 and 15, where means for monitoring magnitude of dielectric properties involves measuring voltage standing wave ratio in feed line to tap.

22. Apparatus according to claim 1, where said magnitudes of said dielectric properties ares mainly those of the capacitive facet of the dielectric property as at each simultaneous measurement frequency.

23. Apparatus according to claim 1, where said magnitudes of said dielectric properties are mainly those of the conductive facet of the dielectric property as at each simultaneous measurement frequency.

24. Apparatus according to claim 1, where said magnitudes of said dielectric properties are dependent on both capacitive and conductive facets of sample.

25. Apparatus according to claim 1, wherein said means for correlating physical and/or chemical properties of sample from said magnitude of comparison of dielectric property at one of simultaneous frequencies with that at other(s) is achieved by internal electronic circuit.

26. Apparatus according to claim 1, where correlation of said physical and/or chemical sample properties from said simultaneous comparison of magnitude of dielectric property at one measured frequency with alternative external entry parameter employs an electronic cicuit for manual entry of said alternative parameter.

27. Apparatus according to claim 1 and claim 26, as per claim 26 ,except where said electronic circuit permits the automatic entry of said alternative parameter from an external source e.g. cell counter and/or haemoglobinometer

28. Appparatus as in claim 1, operated in a differential mode.

29. Apparatus according to claim 1 where the said preferably two or more frequencies may be close to or within the sample dielectric Beta dispersion frequency band.

30. Apparatus according to claim 1 above, capable of use with blood.

31. Apparatus according to claim 1, capable of use with any blood fraction and /or component.

32. Apparatus according to claims 1 and 30, wherein the correlate parameter is any or all of the following: red cell count (r.b.c.); mean cell volume (m.c.v.); haemoglobin content (Hb) ; fibrinogen content or any or all of fibrinogen related parameters namely; p.v , c-reactive protein and i.s.r. (instantly predicted erythrocyte sedimentation rate).

33. Apparatus according to claim 1 capable of use with biofluid other than blood.

34. Apparatus according to claim 1 capable of use with liquid other than biofluid.

35. Apparatus according to claims 1 and 30 but where the output is scaled in arbitary units of "general health status indication".

36. Apparatus according to claim 1 capable of using a sample composite comprising a liquid of constant physical , chemical and dielectric property and an insulating tube /holder where thus the said correlate becomes a physical dimension of the tube and /or holder.

37. Apparatus according to claim 1 where the sample is a digit of the human body.

38. Appartus according to claim 1 where the sample is a limb of the human body.

39. Apparatus as in claim 1 ,but where the frequencies are applied as fast frequency steps or sweeps rather than simultaneously and thus wherein said correlation output will suffer a slight time delay and hence be described as psuedo instantaneous.

40. Apparatus as in claim 1 ,but where the said frequencies are all applied through a single electrode.

41. Apparatus as in claim 1 , but where the said frequencies are all applied through a single inductor.

42. Apparatus as in claim 1 capable of use with a sample where protein concentration is assessed by its effects on the position and magnitude of the high frequency tail of the beta dispersion.

43. Apparatus as in claim 1 where digital and analogue methods are employed.

44. Apparatus as in claim 1 wherein phase sensitive detection is employed.

45. Apparatus as in claim 1 but wherein the said chosen measuring cell is fabricated as a probe.

STATEMENT UNDER ARTICLE 19

Various claims have been amended , extra claims 2-5 and 39 - 45 have been added. Most importantly, changes have been made to claim 1 which it is felt, together with the new claims 2-5 , ought now to distinguish this present invention more fully from those of the prior art. The changes and amendments do not draw upon anything which is not in concept contained in the full present description. In the new claim 2, the " instant" nature of the determination is highlighted as is , the "contactless nature",in new claim 3, i:e, use of this invention without direct electrical contact to the sample has been emphasised, to distinguish it from those citations of the International Search Report where contact is made to a sample where that sample is respectively blood and a human finger and the respective citations concerned are : FR, A, 2 201 762 and Proceedings of the Annual Conference of the IEEE Engineering in Medicine and Biology Society, vol . 10 , November 1988, New Orleans , pp 761-762. Importantly, claim 1 has been amended to show that this invention has an integral measuring cell as part of the apparatus thus to distinguish it from cited apparatus which does not use measuring cells and unlike the current invention , have antennas for remote investigation of biological targets such as : US,A, 4 135 131 and US, ,A, 3 483 860 as have also been cited in the International Search report. Furthermore in the amended claim 1 the technical aspects of this present invention have been clarified with regard to the number of applied frequencies and input /output parameters required for the correlation of sample properties to show by implication from lines 5-13 of the new claim 1 that the invention may correlate the sample properties from dielectric properties

dependent on the application of multiple measurement frequencies two or more in number , see also page 8 , line 16 of the original description and/or by the use of a single frequency or one or more frequencies together with the use of the said externally entered parameter , see page 8 lines 18-22 , page 10, lines 18 -25 and figure 9. It was assumed that the original wording of claim 1 carried the same meaning , i:e that this was a condensed way of making the same statement but obviously it was phrased in such a way that the Search unearthed several single frequency resonance Q techniques namely: GB, A, 2 130 728; GB ,A, 595 720 ; GB, A, 2 248 301; FR, A, 2 378 282 and EP , A, 0 157 496 which do not of course have the added advantage of the said externally entered parameter and thus it is hoped these differences, now clarified , establish sufficent difference to the prior art. Finally the working frequency range of the present invention has been included in the alternative claim 4, see also pages 10,13,17 and 21 of the existing description, to more fully distinguish this invention from those of the International Search Report which employ different frequencies and different hardware for the application of those frequencies than those of the present invention e:g, those cited which employ microwaves in the range 1-100 GHz applied either by cavities, antennas or waveguides as single or swept frequencies , those citations are namely: US, A, 4 135 131; US , A,3 483 860; GB, A, 1 084 860; DE, A, 3 722 213 ; DE, A, 3 637 549 and US,A, 4 257 001, and to distinguish it from the one which uses substantially lower frequencies to make a time dependent assessment (as opposed to instant as in this present invention) of erythrocyte sedimentation rate, namely WO , A,

Further minor amendments have been made to various other of the claims only drawing on material from the body of the description and not significantly altering the understanding therein. All reference to a method has been removed from original claims 25-34 , now replaced by amended claims numbered 29-38. Additional claims 39-45 have been added.

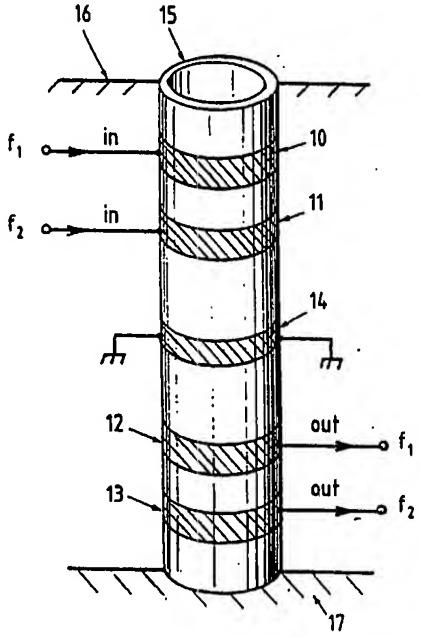


Fig . 1 .

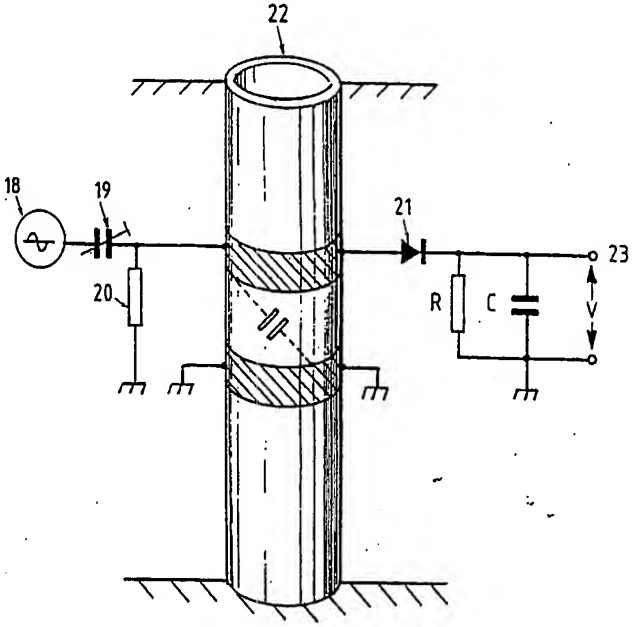


Fig . 2 .

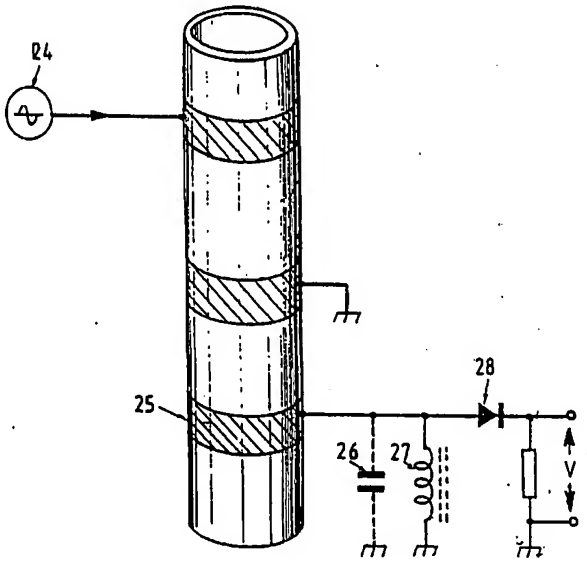


Fig . 3 .

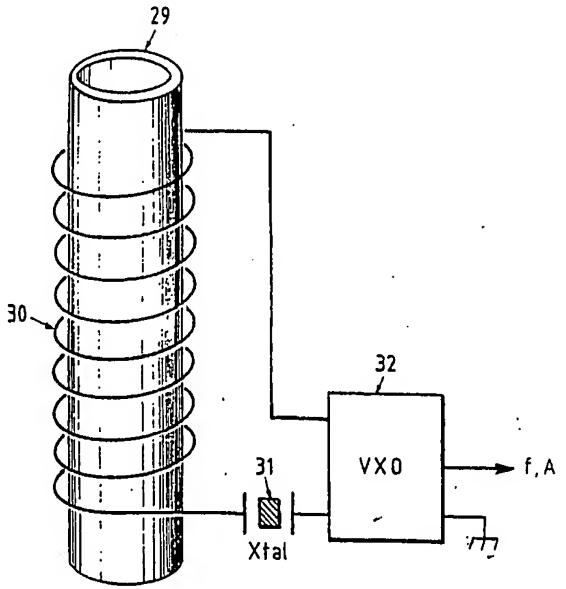


Fig . 4.

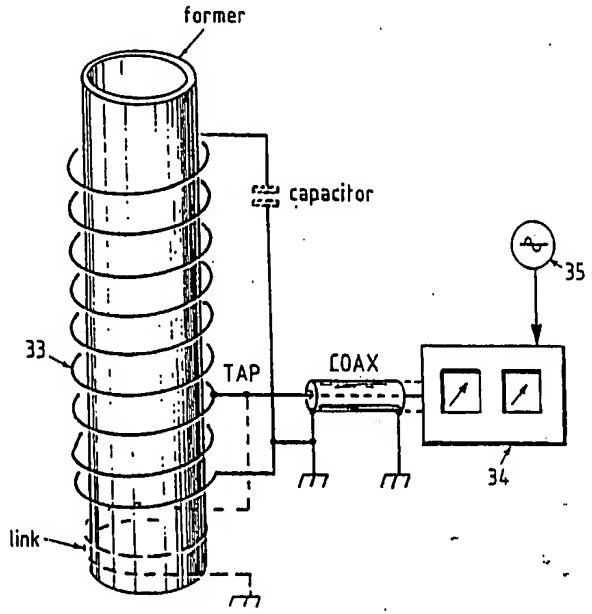

former
capacitor
35
33
TAP
COAX
34
link

Fig . 5.

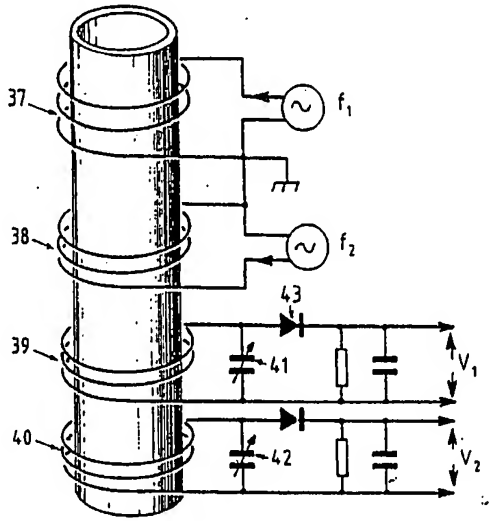

37
38
39
40
f_1
f_2
43
41
42
V_1
V_2

Fig. 6 .

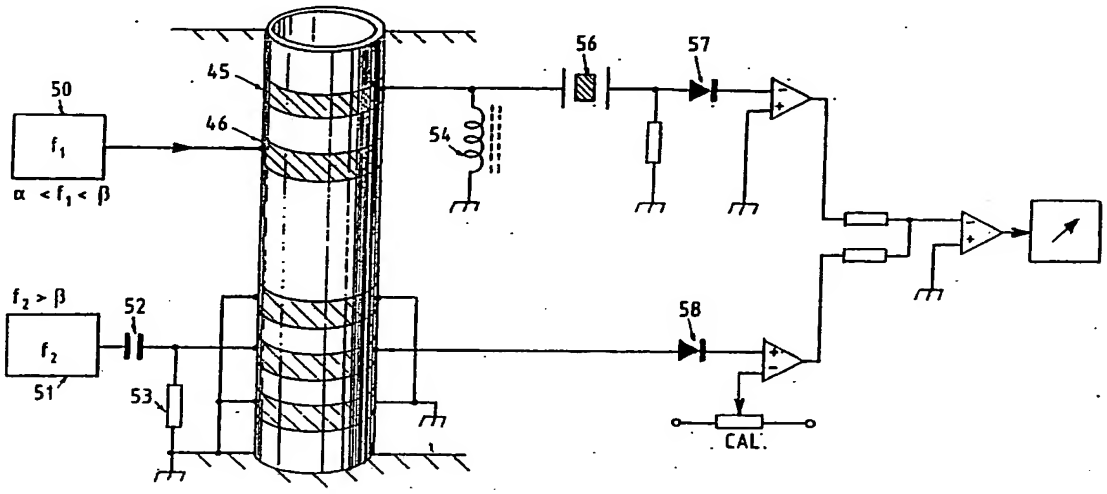


Fig. 7

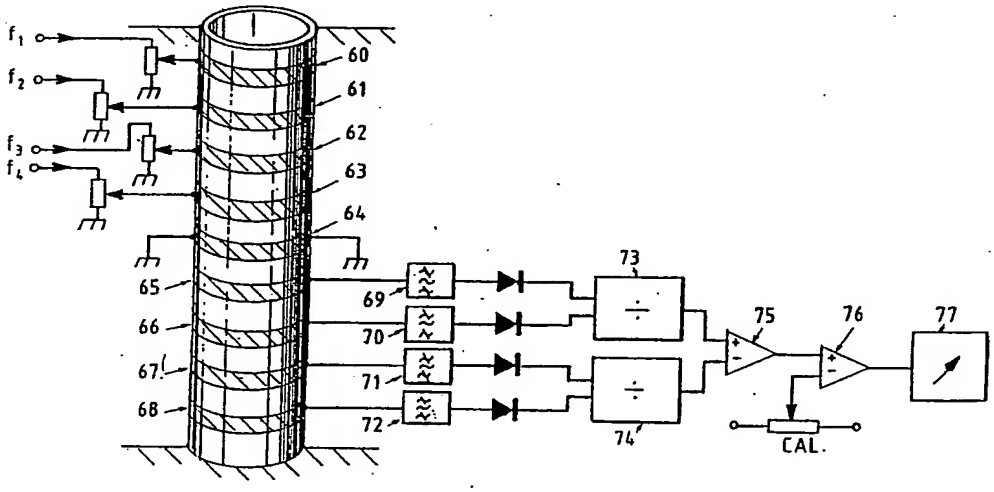


Fig. 8

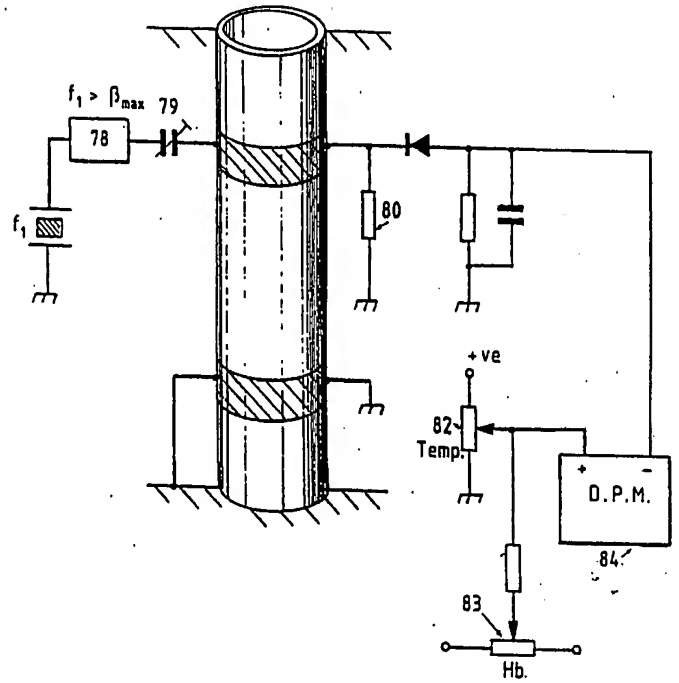

$f_1 > \beta_{max}$
79
78
f_1
80
+ve
82
Temp.
D.P.M.
84
83
Hb.

Fig . 9 .

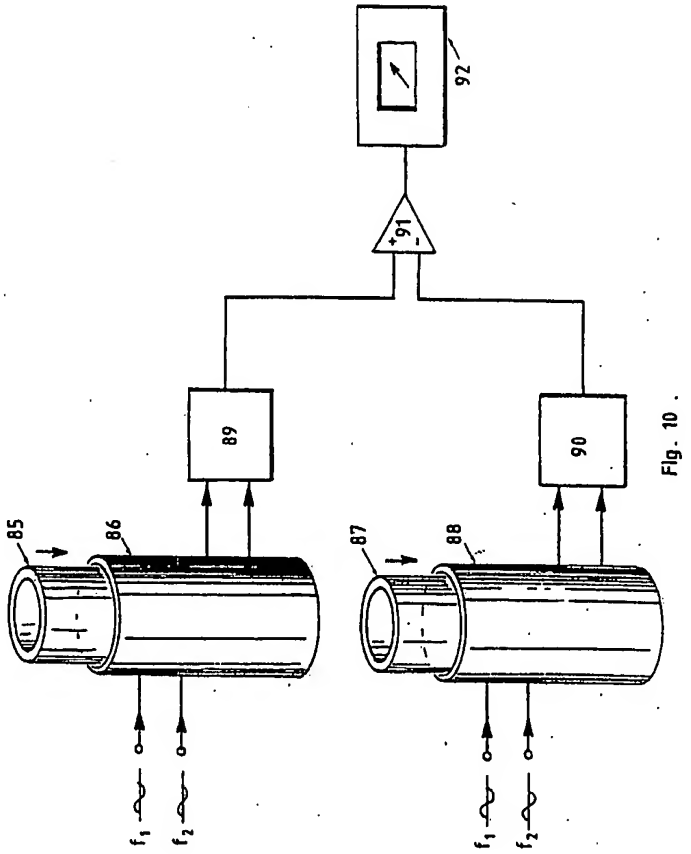

92
91
+
-
89
90
85
86
87
88
f_1
f_2
f_1
f_2

Fig. 10 .

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00475

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 G01N27/22; G01N15/05; G01N22/00; A61B5/05

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	G01N ; A61B

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	GB,A,595 720 (ACE ELECTRONICS LIMITED) 15 December 1947 ---	1-5,8, 12,18, 19,25
X	GB,A,1 084 860 (NILS KAISER) 27 September 1967 see claims 1-12	1,21
A	see page 4, line 49 ---	26
X	GB,A,1 018 188 (NILS KAISER) 26 January 1966 see page 2, line 125 - page 3, line 38; claims 1-9 ---	25-27, 29,30
X	GB,A,2 130 728 (DE BEERS INDUSTRIAL DIAMOND DIVISION) 6 June 1984 see claims 1-5 ---	1,5
	-/--	

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 JUNE 1993	29.06.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN DEN BULCKE E.J.

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No PCT/GB 93/00475

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	FR,A,2 201 762 (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE) 26 April 1974 see claims 1-13 ---	1,12, 25-28
X	US,A,4 257 001 (L.D.PARTAIN ET AL.) 17 March 1981 see claims 1-34 ---	1,25
X	WO,A,9 109 295 (ERIKSSON) 27 June 1991 see claims 1-15 ---	1,4,18, 25-28
X	DE,A,3 722 213 (WEBER KLAUS) 12 January 1989 see column 1, line 1 - line 19 ---	25
P,X	GB,A,2 248 301 (ICI) 1 April 1992 see page 18 ---	1,25
X	EP,A,0 157 496 (NORTHERN TELECOM LIMITED) 9 October 1985 ---	1,5,25
X	FR,A,2 378 282 (LABORA MANNHEIM G.M.B.H.) 18 August 1978 see claims 1-4 ---	1
X	DE,A,3 637 549 (H.ROSENBERGER) 11 May 1988 see column 1 - column 2 ---	1,25,26
X	US,A,3 483 860 (N.STANLEY) 16 December 1969 see claims 1-3 ---	25,26
X	PROCEEDINGS OF THE ANNUAL INTERNATIONAL CONFERENCE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY vol. 10, November 1988, NEW ORLEANS pages 761 - 762 J.M. MCKEE ET AL. 'RADIOFREQUENCY FINGER IMPEDANCE MEASUREMENTS' see page 761 - page 762 ---	1,25,32, 33
X	US,A,4 135 131 (L.E.LARSEN) 16 January 1979 -----	1,25

Form PCT/ISA/210 (extra sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300475
SA 70982

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 18/06/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-595720		None		
GB-A-1084860		None		
GB-A-1018188		NL-A-	286676	
GB-A-2130728	06-06-84	AU-B-	566766	29-10-87
		AU-A-	1916683	29-03-84
FR-A-2201762	26-04-74	None		
US-A-4257001	17-03-81	None		
WO-A-9109295	27-06-91	SE-B-	465140	29-07-91
		EP-A-	0505432	30-09-92
		SE-A-	8904207	14-06-91
DE-A-3722213	12-01-89	None		
GB-A-2248301	01-04-92	None		
EP-A-0157496	09-10-85	JP-A-	60218061	31-10-85
FR-A-2378282	18-08-78	DE-A-	2702557	27-07-78
		GB-A-	1574681	10-09-80
		JP-A-	53093684	16-08-78
		SE-A-	7800725	23-07-78
		US-A-	4187462	05-02-80
DE-A-3637549	11-05-88	None		
US-A-3483860	16-12-69	None		
US-A-4135131	16-01-79	US-A-	4162500	24-07-79

EPO FORM P0179

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82